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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,109	04/21/2000	DAVID FAIRLIE	10648-0001-0	1786

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	21

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/446,109	FAIRLIE ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17, 18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, IDS, FORMAL DRAWINGS AND STATUS OF THE CLAIMS

1. The information disclosure statement (IDS) and Form PTO-1449 filed 7/25/02 and 8/21/02, the amendment, remarks and the formal drawings filed 10/1/02, respectively are acknowledged, entered and considered. In view of Applicant's request claims 1, 5, 8, 13-14, and 21 have been amended. Thus, claims 1-23 are now pending in the application.

With respect to IDS and Form PTO-1449, filed 7/25/02 and 8/21/02 (i.e. Papers Nos. 17 and 18, respectively), the IDS and Form PTO-1449 are identical of each other. Thus, the IDS and Form PTO-1449 filed 7/27/02 have been considered and the IDS and Form PTO-1449 filed 8/21/02 are kept in the file of the instant application as duplicates. The objection to the abstract and the reaction under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment and remarks filed 10/1/02. However, the rejection under 35 U.S.C. 112, first paragraph is maintained for same reasons discussed on the previous Office action as reiterated below:

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical formulations of cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof, does not reasonably provide enablement for pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared *per* the factors indicated in the decision *In re Wands*, 8 USPQ2 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and

8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and state of the prior art in the assessment of undue experimentation.

1) the nature of the invention;

The instantly claimed invention is directed to a pharmaceutical formulation comprising C5a antagonists or agonists with the dimensions defined by co-ordinates A, B, C and D and a method for treatment of a pathological condition mediated by a G protein-coupled receptor in patients by administering therapeutically effective amount of said formulation thereof.

2) the breadth of the claims;

The scope of the claims include pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification does not disclose one reasonable method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. The specification lacks guidance/direction as to how to employ a pharmaceutical preparation useful for treatment of a pathological condition mediated by a G protein-receptor by administering to a patient an effective amount of a compound according to claim 1 in the manner claimed in claims 21-23.

Further, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438,

1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

3) the predictability or unpredictability of the art;

As acknowledged by Applicant on British Journal of Pharmacology, Vol. 128, pp. 1461-1466, 1999 (Applicants own work because out of 9 authors, 4 of them are the inventors of the instant application), the reference shows the pharmaceutical characterization of antagonists of the C5a receptor. On page 1461, right column, the reference states that until recently, no potent or selective small molecule antagonists have been available to evaluate therapeutic effects of blocking C5aRs. Although, C5aRs antagonists are now available for testing and further development, to date, no studies have reported on either the pharmacological nature of the antagonism or on their activities on cells other than PMNs. Further, on the abstract, the reference summarizes the result by stating that these antagonists are insurmountable in nature against C5a for C5aR on at least two human cell types, and the differences in relative receptor binding affinities and antagonistic potencies against C5a are consistent with differences in receptors within these cell types. The nature of these differences is yet to be elucidated, and concludes on page 1465 by stating that the results of the present study indicate the feaasiblity of such a notion. Thus, clearly showing the unpredictable nature of compounds in the method of treatment claimed.

4) the amount of direction or guidance presented;

The specification teaches pharmaceutical formulations comprising cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof as shown in Examples 1-8, Figures 2-10 and Tables 3-4. Example 1 and Table 4 teach synthesis of cyclic peptide, and Figures 2-4 and 7, Table 3 and Example 2 demonstrate NMR structure determination of cyclic antagonists. Figures 5-6 and Examples 3-6 show *in vitro* receptor-binding assay. Figures 8-10 and Examples 7-8 describe the *in vivo* assays of anti-inflammatory activity on rats in which paw oedema is determined by administering the carrageenan compound into the air pouch and exudate is collected and the anti-inflammatory effects is assayed by differential counting of cells in the air-pouch exudate.

6) the quantity of experimentation necessary;

The claimed invention is directed to pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid

arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. However, the phrases "cyclic agonists and antagonists" and "constrained acyclic structure" are not justified by the limited exemplary disclosure of using pharmaceutical formulations comprising cyclic peptides of formulae II or IV and the linear derivatives described which are improperly incorporated by references on page 9, lines 22-37 in the instant invention. Further, there is no working example or data or evidence which shows that the claimed compounds are useful as pharmaceutical formulations in the method of treatments as claimed in claims 21-23. Although, there is preparation Examples for pharmaceutical formulations as well as *in vitro* and *in vivo* assays and certain mode of administration. Nevertheless, there is no evidence in the instant specification to use or administer the pharmaceutical formulations in therapeutically effective amount as claimed, except for the mere recitation of protocols on page 19 in the instant specification contemplating the suitable dosage of the compound to be administered generally in mammals for the intended treatment of all kinds of pathological conditions mediated by a G protein-coupled receptor. Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical formulations of claim 20 in the manner claimed in claims 21-23. Hence, the only support for the claimed pharmaceutical formulations in the specification and method of treatment thereof is Applicant's

supposition of the invention as recited in the protocols. Thus, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since **all kinds** of pharmaceutical formulations comprising the various compounds in a method for treatment of a pathological condition mediated by a G protein-coupled receptor, such as rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. in a mammal are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which are not clearly disclosed. Hence, one of ordinary skill in the art would not be able reproduce all the aspects the claimed invention pharmaceutical formulations as well as methods for treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a affecting the pathological conditions, such as rheumatoid arthritis, ARDS, septic shock, Alzheimer's disease, ect., as encompassed in the claims would be effective and under what conditions.

7) the state of the prior art;

Thus, in view of the above and in view of the fact that the state of the prior art as discussed above, at the time the invention was made there was no pharmaceutical

characterization of antagonists of the C5a receptor; and as to date (i.e 1999-date of publication of the reference), no studies have reported on either the pharmacological nature of the antagonism or on their activities on cells other than PMNs, let alone administering an effective amount of pharmaceutical formulation of the claimed compound to treat all kinds of pathological conditions mediated by a G protein-coupled receptor in the manner claimed in claims 21-23.

8) the relative skill of those skilled in the art;

Therefore, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Thus, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims; the claims are not commensurate in scope with the enabling disclosure. Hence, in consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teachings, and guidance presented. Therefore, absent factual data to the contrary, the amount and level of experimentation needed is undue. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. 112 [1st] PARAGRAPH.

3. The rejection of claims 1-23 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical formulations of cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof, does not reasonably provide enablement for pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments and the several publications attached herewith to confirm the predictability of the animal models and further to demonstrate the efficacy of the claimed compounds filed 10/1/02 have been fully considered but they are not persuasive. Applicant has argued that 1) the Examiner has not made a *prima facie* case for lack of enablement; 2) even if one assumes hypothetically that a *prima facie* case has been made, the rejection is effectively rebutted by Applicant's remarks and the enclosed attached publications; 3) the legal standard imposed by 35 U.S.C. § 112, first paragraph has been met because Applicant through detailed objective guidance provide sufficient teachings for one of skilled in the art to make the compounds consistent with the scope of the claimed compounds, which include general methods of amino acid and peptide synthesis as disclosed on pages 22-23 in the instant specification and as supported by the attached publications; 4) no working examples are required in a specification in order for it to meet the requirements of § 112, first paragraph for administering the compounds as taught, and as such, there is insufficient evidence to support the rejection as set forth in the Official Action, that one having ordinary skill in the art could practice the claimed invention without undue experimentation; and 5) concludes by stating that the specification provides a full disclosure of the invention with respect of how to make and use the invention, there is additional evidence consistent with description in the specification which enables the full scope of the present invention, and as such, the claims are, in fact, fully enabled by the specification as originally filed, and that the requirements of the first paragraph of 35 U.S.C. § 112 have been met is not persuasive.

Contrary to Applicant's arguments, there is no evidence in the instant specification to use or administer the pharmaceutical formulation in therapeutically effective composition as claimed. The publications provided have been considered and appears to support the disclosure in enabling for pharmaceutical formulations of cyclic peptides of formula II or IV, or the linear derivatives of compounds 1-7 or compounds 8-10 which display reduced biological activity and a method for *in vitro* comparison of receptor-binding and antagonist activity with hexapeptide compound 7 and *in vivo* activity of cyclic C5a antagonist in rats by using the above pharmaceutical formulations thereof. The Examiner agrees that the attached publications confirm that the instant specification in Examples 1-8, Figures 2-10 and Tables 3-4. Example 1 and Table 4 teach synthesis of cyclic peptide, and Figures 2-4 and 7, Table 3 and Example 2 demonstrate NMR structure determination of cyclic antagonists. Figures 5-6 and Examples 3-6 show *in vitro* receptor-binding assay. Figures 8-10 and Examples 7-8 describe the *in vivo* assays of anti-inflammatory activity on rats in which paw oedema is determined by administering the carrageenan compound into the air pouch and exudate is collected and the anti-inflammatory effects is assayed by differential counting of cells in the air-pouch exudate. However, the scope of the instantly claimed invention are very broad and speculative in that there is/are no working example(s) or data or evidence which shows that the claimed pharmaceutical formulation comprising C5a antagonists or agonists with the dimensions defined by co-ordinates A, B, C and D and a method for treatment of a pathological condition mediated by a G protein-coupled receptor in patients by administering therapeutically effective amount of said formulation thereof.

The scope of the claims include pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. The specification nor the attached publications intended to support the claimed invention disclose one reasonable method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. The specification including the publications provided to support the enablement issue lacks guidance/direction as to how to employ a pharmaceutical preparation useful for treatment of a pathological condition mediated by a G protein-receptor by administering to a patient an effective amount of a compound according to claim 1 in the manner claimed in claims 21-23.

With respect to the predictability or unpredictable nature of the claimed compound, Applicant has argued on page 5 of the remarks filed 10/1/02 (Paper No. 19) that Paczkowski et al. reference speculate based on unspecified and unknown differences there may be two types of

C5a receptors and the reference provides no evidence to support this speculation. However, contrary to Applicant's arguments as acknowledged by Applicant on British Journal of Pharmacology, Vol. 128, pp. 1461-1466, 1999 (Applicants own work because out of 9 authors, 4 of them are the inventors of the instant application), in which the reference shows the pharmaceutical characterization of antagonists of the C5a receptor. On page 1461, right column, the reference states that until recently, no potent or selective small molecule antagonists have been available to evaluate therapeutic effects of blocking C5aRs. Although, C5aRs antagonists are now available for testing and further development, to date, no studies have reported on either the pharmacological nature of the antagonism or on their activities on cells other than PMNs. Further, on the abstract, the reference summarizes the result by stating that these antagonists are insurmountable in nature against C5a for C5aR on at least two human cell types, and the differences in relative receptor binding affinities and antagonistic potencies against C5a are consistent with differences in receptors within these cell types. The nature of these differences is yet to be elucidated, and concludes on page 1465 by stating that the results of the present study indicate the feaasiblity of such a notion. Thus, clearly showing the unpredictable nature of compounds in the method of treatment claimed.

Thus, in view of the above and in view of the fact that the state of the prior art as discussed above, at the time the invention was made there was no pharmaceutical characterization of antagonists of the C5a receptor; and as to date (i.e 1999-date of publication of the reference), no studies have reported on either the pharmacological nature of the antagonism

or on their activities on cells other than PMNs, let alone administering an effective amount of pharmaceutical formulation of the claimed compound to treat all kinds of pathological conditions mediated by a G protein-coupled receptor in the manner claimed in claims 21-23.

Furthermore, The claimed invention is directed to pharmaceutical formulations comprising all kinds of antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to the dimensions defined by co-ordinates A, B, C, and D as recited in independent claims 1 and 15; and to methods of treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a, and wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. by administering the above pharmaceutical formulations thereof as claimed in claims 21-23. However, the phrases "cyclic agonists and antagonists" and "constrained acyclic structure" are not justified by the limited exemplary disclosure of using pharmaceutical formulations comprising cyclic peptides of formulae II or IV and the linear derivatives described which are improperly incorporated by references on page 9, lines 22-37 in the instant invention. Further, there is no working example or data or evidence which shows that the claimed compounds are useful as pharmaceutical formulations in the method of treatments as claimed in claims 21-23. Although, there is preparation Examples for

pharmaceutical formulations as well as *in vitro* and *in vivo* assays and certain mode of administration. Nevertheless, there is no evidence in the instant specification nor in the publications provided to use or administer the pharmaceutical formulations in therapeutically effective amount as claimed, except for the mere recitation of protocols on page 19 in the instant specification contemplating the suitable dosage of the compound to be administered generally in mammals for the intended treatment of all kinds of pathological conditions mediated by a G protein-coupled receptor. Further, there are no sufficient data or evidence to substantiate such protocols of using pharmaceutical formulations of claim 20 in the manner claimed in claims 21-23. Hence, the only support for the claimed pharmaceutical formulations in the specification and method of treatment thereof is Applicant's supposition of the invention as recited in the protocols. Thus, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since **all kinds** of pharmaceutical formulations comprising the various compounds in a method for treatment of a pathological condition mediated by a G protein-coupled receptor, such as rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome, etc. in a mammal are contemplated and are encompassed as well as wide range of situations. The results desired appear

to be highly dependent on all variables, the relationship of which are not clearly disclosed. Hence, one of ordinary skill in the art would not be able reproduce all the aspects the claimed invention pharmaceutical formulations as well as methods for treatment of a pathological condition mediated by a G protein-coupled receptor involving over expression or under expression of C5a affecting the pathological conditions, such as rheumatoid arthritis, ARDS, septic shock, Alzheimer's disease, ect., as encompassed in the claims would be effective and under what conditions.

Therefore, in view of the above, the scope of the pharmaceutical formulation with various cyclic or constrained acyclic compounds which modulate the activity of G protein-coupled receptors and are useful in the treatment of conditions mediated by G protein-coupled receptors having all kinds of modifications intended to be effective for the claimed purpose as encompassed in the claims would be effective and under what conditions. The Examiner is unable to determine the enablement of the invention as claimed without appropriate working examples. The only support for the claimed invention in the specification is Applicant's supposition of the invention and the improper incorporation of several publications attached herewith supporting the protocols disclosed in the instant specification. Secondly, the Examiner has clearly shown in the previous Office Action of Paper No. 16 (mailed 5/6/02) and as discussed above that without guidance through working example(s), one of ordinary skill in the art would not predict from background discussion and/or information and protocols to employ or administer the pharmaceutical formulation in therapeutically effective composition in the manner

claimed. Thus, the specification does not enable any person skilled in the art to which it pertains, or which it is most nearly connected, to use the invention commensurate in scope with the claims. In the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention. Thirdly, it is not understood from Applicant's response how the instant invention, which Applicant considers as novel and inventive, be exemplified without working example(s) or data or evidence. The law requires that a disclosure in an application shall inform those skilled in the art how to use Applicant's alleged discovery, not how to find out how to use it for themselves. See *In re Gardner et al.*, 166 USPQ 138 (CCPA 1970). Therefore, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled. Hence, it is viewed that the specification does not enable the invention as claimed in claims 1-23, as it does not teach how to use the invention to achieve the function of the claims for the reasons discussed above. Thus, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is again suggested.

ACTION IS FINAL

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Mohamed/AAM

December 24, 2002